

Review



The Complex Tail of Circulating Sphingolipids in Atherosclerosis and Cardiovascular Disease

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ABSTRACT

Sphingolipids (SLs) are critical players in a number of cellular processes and have recently been implicated in a large number of human diseases, including atherosclerosis and cardiovascular disease (CVD). SLs are generated intracellularly in a stepwise manner, starting with the generation of the sphingoid long chain base (LCB), followed by *N*-acylation of the LCB to form ceramide, which can be subsequently metabolized to sphingomyelin and glycosphingolipids. Fatty acids, which are taken up by cells prior to their activation to fatty acyl-CoAs, are used in 2 of these enzymatic steps, including by ceramide synthases, which use fatty acyl-CoAs of different chain lengths to generate ceramides with different *N*-acyl chain lengths. Recently, alterations in plasma ceramides with specific *N*-acyl chain lengths and degrees of saturation have emerged as novel biomarkers for the prediction of atherosclerosis and overall cardiovascular risk in the general population. We briefly review the sources of plasma SLs in atherosclerosis, the roles of SLs in CVD, and the possible use of the “ceramide score” as a prognostic marker for CVD.

Keywords: Sphingolipids; Ceramide; Biomarkers; Atherosclerosis; Acyl chain

INTRODUCTION

Sphingolipids (SLs) have been implicated in many human diseases, including cancer,^{1,2} epilepsy,³ cystic fibrosis,⁴ metabolic disorders,⁵ and cardiovascular disease (CVD).^{6,7} A number of recent independent studies using relatively large patient cohorts^{8,9} have demonstrated that levels of the simplest SL, namely ceramide, are altered in the plasma prior to the appearance of atherosclerosis and CVD. These studies suggest that ceramides with specific *N*-acyl chain lengths might be useful as biomarkers of arterial plaque instability and CVD.⁸

Since CVD is a major cause of death in the western world, the discovery that plasma ceramide levels might be predictive of disease development has had a major impact on the world of SL research. Little is currently known about the source of plasma ceramides, or about the biochemical mechanisms that link plasma ceramides with CVD. Since ceramide is a highly hydrophobic molecule, it is not soluble in aqueous media and is found in the plasma either bound to carrier proteins or to lipid-protein complexes such as lipoproteins. Although

lipoprotein biology is well studied, little information is available regarding the mechanisms by which ceramide is incorporated into lipoproteins, or about its precise role in lipoproteins. Consequently, in the current short review we first discuss the biochemistry of SLs, focusing largely on how the acyl chain diversity of SLs is generated. We then discuss the possible origins of plasma SLs and their involvement in atherosclerosis, and the use of ceramide as a novel CVD biomarker. We conclude that data accumulated in the past few years are consistent with the relatively unexplored notion that manipulation of the ceramide pathway^{10,11} may pave the way for novel therapeutic approaches for atherosclerosis and CVD.

THE ACYL CHAIN COMPLEXITY OF SLs

The 3 major structural moieties of SLs include i) the sphingoid long chain base (LCB) to which ii) an acyl chain is attached through an amide bond, and iii) the various head groups that are attached at C1. Each of these structural moieties can vary significantly, to the point that ~4,000 distinct SL structures have been curated to date (<http://www.lipidmaps.org>). SL levels are generated and maintained in the cell via a combination of metabolic regulation through the SL anabolic and catabolic pathways¹² and the turnover of these lipids in signaling pathways.¹³

SL synthesis begins with the synthesis of the sphingoid LCB, sphinganine, via 2 consecutive enzymatic steps, namely serine palmitoyltransferase and 3-ketosphinganine reductase. *N*-acylation of the LCB produces dihydroceramide, which is subsequently desaturated via dihydroceramide desaturase to form ceramide, the backbone of all complex SLs. The *N*-acylation of both sphinganine (in the anabolic pathway) and of sphingosine (in the catabolic pathway) is catalyzed by ceramide synthase (CerS), an enzyme located in the membrane of the endoplasmic reticulum (ER) (**Fig. 1**). One of the most exciting discoveries in the field of SL metabolism in the past couple of decades was the molecular identification of 6 mammalian CerS isoforms, with each differing in their ability to use acyl chains of various lengths as substrate, as reviewed by Zelnik et al.¹⁴ The acyl chain moiety is provided by cytosolic acyl-CoAs,¹⁵ which generally contain 14–32 carbons with different degrees of saturation.^{16,17} The acyl chain binding protein facilitates the synthesis of very-long acyl chain ceramides by delivering acyl-CoAs to CerS (**Fig. 1**).¹⁵

Following their synthesis in the ER, ceramides are transported to the Golgi apparatus via protein- or vesicular-mediated transport mechanisms where they are metabolized to either sphingomyelin (SM) or glucosylceramide (GlcCer) and subsequently to more complex glycosphingolipids (GSLs).¹⁸ There is no evidence for remodeling of the SL *N*-acyl chain once it has been incorporated into ceramide, indicating that the *N*-acyl chain length of SLs is determined in the ER by CerS. Moreover, different cells and different tissues have a unique pattern of SLs with specific *N*-acyl chain lengths, although this distribution does not always correlate with the levels of CerS,¹⁹ leading to the suggestion that more complex mechanisms of regulation of CerS activity exist, such as dimer formation²⁰ and phosphorylation.²¹

One potential means to regulate the cellular acyl chain composition of ceramides is the bioavailability of acyl-CoAs. Acyl-CoAs originate from circulating fatty acids that are taken up by cells via fatty acid translocases such as FAT/CD36, very-long chain fatty acyl-CoA synthetases, and caveolin-1.²² Acyl-CoAs, which are generated via acyl-CoA synthetases (ACS)²³⁻²⁵ (**Fig. 1**), are used for energy production via β -oxidation²⁶ and as substrates for the

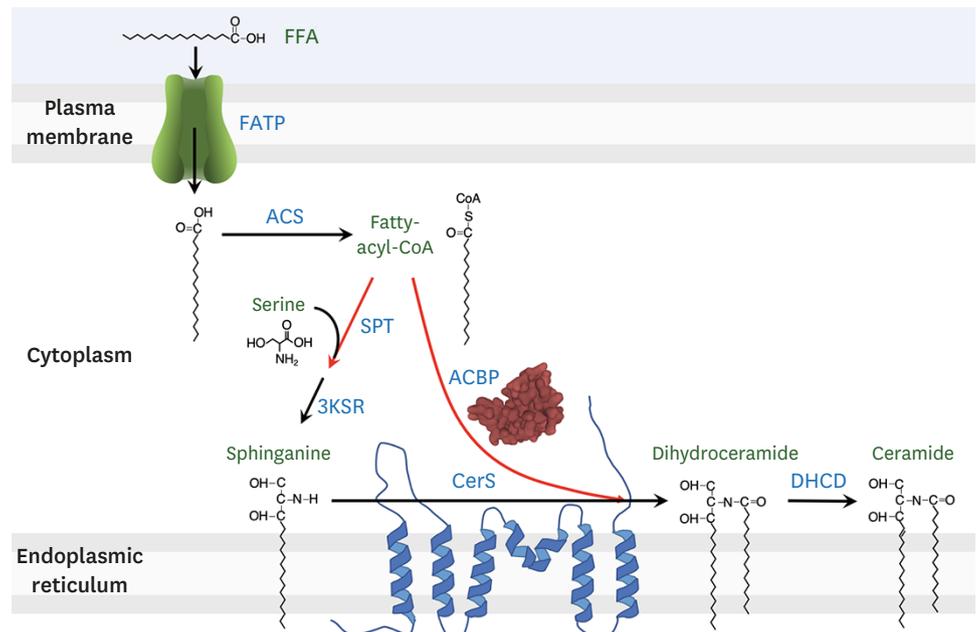


Fig. 1. Fatty acyl-CoAs are required for 2 steps of SL synthesis. Free fatty acids are taken-up by cells via FATP and subsequently activated via acyl-CoA synthetase. Fatty acyl-CoAs are then used for 2 steps (red) of SL synthesis, with the *N*-acyl chain of ceramide determined by the specificity of CerS. Proteins are shown in blue and lipids in green. FFA, free fatty acid; FATP, fatty acid transport protein; ACS, acyl-CoA synthetase; SPT, serine palmitoyltransferase; 3KSR, 3-ketosphinganine reductase; ACBP, acyl-CoA binding protein; CerS, ceramide synthase; DHCD, dihydroceramide desaturase; SL, sphingolipid.

synthesis of various complex lipids including triacylglycerols, phospholipids, cholesterol esters and SLs.²⁷⁻²⁹ Twenty-six mammalian ACSs have been identified²⁸ and classified according to their substrate specificity for various lengths of fatty acids. Thus, short-chain ACSs prefer fatty acids of 2–4 carbons, medium-chain ACSs use C6–C10 fatty acids, long-chain ACSs can activate fatty acids of 12–20 carbons, and very-long chain ACSs, also referred to as fatty acid transport proteins, prefer C16 and C18 fatty acids although they can also utilize fatty acids of 20 carbons and higher. Thus, the acyl-CoA composition of ceramide likely depends on a combination of the activity of CerS and of ACSs.

THE SOURCES AND TYPES OF PLASMA SLs

More than 230 SL species have been identified in human plasma,³⁰ accounting for ~5% of the plasma lipidome.³¹ SM comprises the vast majority (~80%) of circulating SLs, with most being d18:1/C16:0-SM, while ceramide accounts for < 3%,³¹ comprising mainly very-long acyl chain ceramides (i.e. C24:0 and C24:1).³⁰⁻³²

SLs in plasma, like other plasma lipids, likely arise from 2 sources, namely the liver and exogenous sources after absorption via the intestine. Concerning the latter, SLs are a minor constituent of animal-based foods, including meat, milk, eggs, and aquatic products, and are also found in plant-based foods.³³ Unlike some fatty acids,³⁴ there is no evidence that SLs are essential (i.e., that they cannot be synthesized but rather need to be taken up through the diet). There is a relative paucity of data on the intake of dietary SLs, although an average individual in the USA has been estimated to consume ~380 mg of SLs per day,³⁵ whereas a study in Japan reported consumption of 45–292 mg of SLs per day³⁶ depending on caloric intake.

SL absorption has been analyzed in a number of studies by the use of radiolabeled or stable isotope-labeled SLs. For instance, upon feeding rats with deuterated ceramide, radioactivity was distributed throughout a number of tissues³⁷; however, this accounted for only ~5% of the applied radioactivity. Furthermore, no attempts were made to identify the SL (or other lipid) species into which the radioactivity was distributed, limiting the conclusions of this study to a demonstration that a minimal amount of the deuterated ceramide is indeed absorbed in the gastrointestinal tract. In a follow-up study, upon feeding mice with deuterated sphingosine,³⁸ 35% of the consumed lipids were absorbed, although the majority was excreted in the urine. Approximately 5% was detected in tissues, and deuterated SLs (including ceramide and GlcCer) were measured in the skin, indicating that absorbed sphingosine can be metabolized to complex SLs subsequent to its uptake. Dietary complex SLs were also absorbed to some extent, with early studies suggesting that ~40% of SM and GSL are excreted in the feces as either the intact lipid or as ceramide and sphingosine.^{39,40}

As a result of these and other studies, it is now accepted that the majority of dietary SLs, such as SM and GSLs, are degraded in the intestine via sphingomyelinases, glucoceramidases or ceramidase^{40,41} to ceramides, sphingosine or fatty acids prior to their absorption into the intestinal mucosa, via unknown mediators.^{39,40,42,43} Consistent with this is the observation that SM consumption does not increase circulating SM levels.⁴⁴ Interestingly, germ-free mice display lower levels of intestinal SM degradation,⁴⁵ leading to the suggestion that microflora may contribute to the catabolic activity in the intestine either by taking an active part in SL metabolism or by modifying metabolism.^{43,46} Mucosal cells are able to generate complex SLs from absorbed LCBs,^{40,47} which are retained in the intestine, or further broken down to fatty acids^{39,42} that can be incorporated into chylomicron triacylglycerols and transported to the lymphatic system.^{48,49} In summary, dietary SLs are metabolized prior to their partial uptake in the intestine, followed by further metabolism within the target tissues. However, the impact of dietary SLs on the plasma SL composition is generally considered to be minimal.^{31,50,51}

As mentioned above, due to their hydrophobicity, circulating SLs are bound to carrier proteins such as albumin or lipoproteins.^{32,52,53} Lipoproteins containing apolipoprotein B (ApoB), such as very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL), are rich in SLs, while high-density lipoprotein (HDL) has lower levels of SLs.³¹ However, since HDLs are found at higher levels than VLDLs, circulating SLs are distributed equally between ApoB lipoproteins and HDLs.³¹

SLs generated in the liver are incorporated into VLDL along with other lipid metabolites, which is facilitated by microsomal triglyceride transfer protein (MTP).⁵⁴ Levels of ceramide and SM in VLDL are higher than in the liver. Moreover, the SM acyl chain length also differs between the liver and VLDL,⁵⁵ suggesting that MTP has an element of acyl chain specificity. In mice defective in MTP, the assembly of both chylomicrons in the intestine and VLDLs in the liver was affected, resulting in a significant reduction of circulating lipids including ceramide and SM;⁵⁶ moreover, ceramides, GSLs, and sphingosine accumulated in the liver but not in the intestine, suggesting that a main entry point for ceramide to the circulation is the liver, where VLDL is synthesized. Levels of both ceramide and SM in chylomicrons (lipoproteins that are assembled in the intestine and facilitate the absorbance of lipids from dietary origin) are lower than those of VLDL and LDL.⁵⁷ These findings strengthen the notion that the majority of SLs found in the plasma originate from the liver rather than from the diet.

SLs IN ATHEROSCLEROSIS AND CVD

Atherosclerosis, which involves the buildup of lipid aggregates and other substances in arterial walls, causes the formation of atheromatous plaques (i.e., plaques in arteries) and arterial stenosis, which can result in coronary artery disease (CAD). Atherosclerosis is one of the main causes of CVD,⁵⁸ with > 30% of deaths worldwide attributed to CVD (WHO and Murphy et al.⁵⁹). The mechanism behind plaque formation has been reviewed elsewhere,^{60,61} but briefly, modified LDL particles interact with arterial walls where they cause an immune response prior to being taken up by macrophages, leading to the formation of foam cells, which cause inflammation and create atheromatous plaques.

A number of pathological features of atherosclerotic plaques, including their lipid composition,^{62,63} are considered a reliable predictor of plaque stability.^{64,65} Measurements of plasma levels of LDL and HDL are the most common means used to predict atherosclerosis^{66,67} and CVD,^{68,69} although LDL and HDL are somewhat limited in their prognostic ability,⁷⁰ suggesting that more credible biomarkers are needed.^{71,74} Recently, largely based on advances in lipidomic analysis, including SL mass spectrometry,^{75,76} additional lipid markers have been proposed,⁷⁷ including ceramides.⁷⁸

The first hint that SLs might be involved in atherosclerotic plaque formation was the finding that SM was abundant in such plaques.⁶² Some 40 years later, a correlation between SM levels and CAD in human patients was observed.⁷⁹ However, in addition to SM, ceramide also accumulates in lesions,⁸⁰ and plasma ceramide levels positively correlate with circulating LDL levels.⁸¹ The source of this ceramide may be plasma SMase, which is elevated⁸² in patients with acute coronary syndrome, and the origin of which appears to be LDL,⁸³ arterial wall cells,^{80,84-86} or human blood monocyte-derived macrophages.^{86,87} During atherogenesis, LDL is retained in arterial walls, where it is susceptible to the action of SMase, thus converting LDL SM into ceramide within lesions and accelerating foam cell formation.^{88,89} In addition, ceramide elevation in LDL correlates with the susceptibility of LDL to aggregate,⁹⁰⁻⁹³ which itself is associated with CAD.⁹⁰ Conformational changes in apolipoprotein B-100 (ApoB-100), the main protein in LDL, mediate this aggregation.^{94,95} Oxidized LDL, which is abundant in atherosclerosis, may stimulate SMase activity.⁹⁶ We suggest that when ceramide is generated in LDL, ceramide domains are formed,⁹² causing biophysical changes in the membrane⁹⁷ that may result in conformational modifications of ApoB-100 and perhaps other apolipoproteins. These structural changes may cause ceramide-driven LDL aggregation (**Fig. 2**), which stimulates their uptake into recruited macrophages and results in formation of foam cells, arterial plaque, and stenosis. In other words, the action of SMase on LDL-SM induces LDL aggregation and foam cell formation; this pathway has emerged as a central atherogenic process that promotes plaque formation and mortality (**Fig. 3**). Furthermore, administration of myriocin, a SL synthesis inhibitor that reduces ceramide and SM levels, decreased the propensity of LDL to aggregate and ameliorated atherosclerotic plaque formation in mice.^{90,98-100} Whether such an approach is feasible in humans¹⁰¹ remains to be tested.

Once LDL aggregates are formed and taken-up by macrophages, foam cells are created, which is an irreversible step. Apolipoprotein E (ApoE),¹⁰² an additional protein common to LDL, can be incorporated into LDL post-assembly and facilitate LDL clearance, and impairment of this mechanism is considered atherogenic.¹⁰³ ApoE preferably binds ceramide-rich LDL, reduces its aggregation, and enhances LDL clearance.^{91,92} SMase activity is increased in LDL with high levels of SM, inducing ApoE binding,⁹¹ suggesting that SMase affects the ability of ApoE to

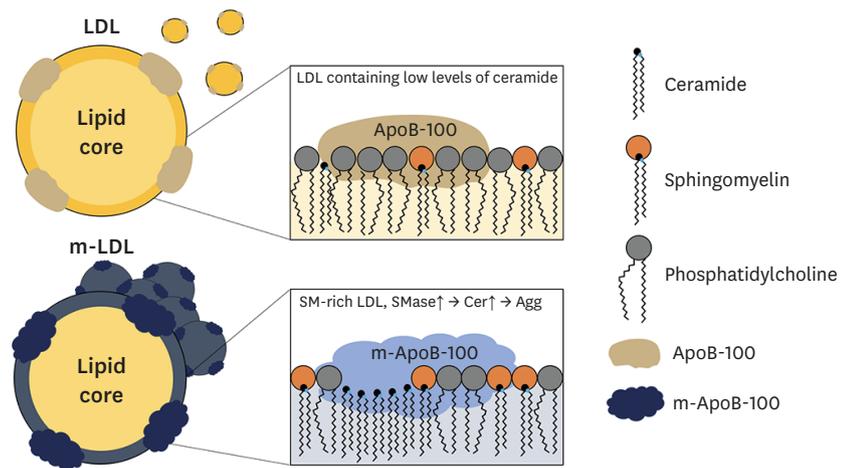


Fig. 2. Schematic representation of SL composition in LDL. LDL can be modified by changing the SL composition as a result of upregulation of SMase activity, accelerating ceramide accumulation and the formation of ceramide domains. These domains trigger a conformational change in ApoB-100 that promotes LDL aggregation. LDL, low-density lipoprotein; SMase, sphingomyelinase; ApoB-100, apolipoproteinB-100; m-ApoB-100, modified apolipoproteinB-100; m-LDL, modified LDL; SM, sphingomyelin; Cer, ceramide; Agg, aggregation; SL, sphingolipid.

induce LDL clearance by macrophages. We suggest that this mechanism can act as a 2-edged sword, whereby high levels of oxidized LDL are found in CAD patients and in patients with a high risk for developing CVD. If ApoE, as a result of elevated ceramide levels, induces LDL uptake, the transformation of macrophages into foam cells will be stimulated and thereby the formation of an atheromatous plaque will be induced. We conclude that ceramide formation in LDL affects atherosclerosis via 2 individual apolipoproteins, causing either a harmful or a protective effect on atheromatous plaque formation.

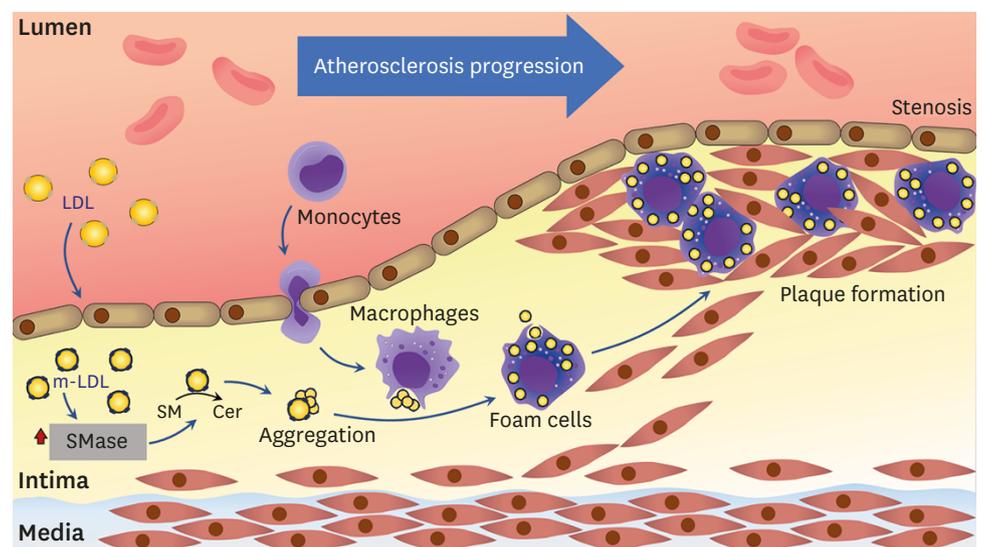


Fig. 3. Spingolipid metabolism in the formation of atheromatous plaques. Scheme of atheromatous plaque formation in the tunica intima and the possible involvement of secreted SMase. SMase, sphingomyelinase; SM, sphingomyelin; Cer, ceramide; LDL, low-density lipoprotein; m-LDL, modified LDL.

SLs AS CVD BIOMARKERS

In recent research, plasma ceramide levels have been suggested to be a more accurate marker of the disposition to CVD than the LDL/HDL ratio. Thus, specific plasma ceramides, namely d18:1/C16:0-, d18:1/C18:0- and d18:1/C24:1-ceramide, appear to be indicative of plaque instability and CVD fatality.^{8,104-106} These ceramide species predict cardiovascular events in asymptomatic individuals⁷⁸. Calculation of the ratio of d18:1/C16:0-ceramide to d18:1/C24:0-ceramide significantly improved CAD prediction.⁸ Thus, a ceramide “risk score” has been generated, in which levels of d18:1/C16:0-, d18:1/C18:0- and d18:1/C24:1-ceramides are calculated along with their ratios versus d18:1/C24:0-ceramide⁸; values above the median or the third quartile contribute to risk categories. The use of the “ceramide score” was further established in a 9-year-long prospective follow-up trial,⁹ in which the ceramide score clearly correlated with the risk of CVD in CAD patients. A score higher by a single standard deviation increased the risk of CVD by 21%–35% and CAD patients with a higher ceramide risk score had an approximately 2-fold higher risk of CVD mortality. A further study¹⁰⁷ confirmed the usefulness of the ceramide score. Finally, products of ceramide metabolism, such as GlcCer (with similar acyl chain lengths to the parent ceramide) also correlate with increased risk^{108,109} and a recent study suggested a novel SL-inclusive CAD risk score that including a wider range of plasma SLs (d18:0/C18:0-, d18:1/C18:0-, d18:1/C22:0-, and d18:1/C24:0-ceramides, d18:0/C24:1-, d18:1/C18:0- and d18:1/C24:0-SM, and sphingosine).¹¹⁰ The reason for the correlation between plasma ceramides and CVD is not totally understood, but many CVD events are a direct result of coronary artery stenosis, which is associated with the same ceramide score as above.¹¹¹ The ceramide score is slowly being introduced into clinical practice.¹¹²

What is the source of changes in plasma ceramides? A number of possibilities can be envisaged that would change the balance between ceramides of different *N*-acyl chain lengths. Ceramide levels could either be regulated by the activity of CerS^{113,114} in the liver or, alternatively, by changes in the catabolic pathway via the action of SMases¹¹⁵ in the plasma and tunica intima. Plasma ceramides in healthy individuals are composed largely of d18:1/C24:0-ceramide (at least in ApoB-containing lipoproteins).³¹ Plasma SM levels are significantly higher than plasma ceramide levels, perhaps suggesting that regulation of SMase activity is likely to be the main factor that mediates plasma ceramide levels, although it is unclear how this would affect the *N*-acyl chain length. Irrespective of the precise mechanism by which the unique pattern of plasma ceramides is generated, analysis of specific ceramide species in plasma may be widely used in the years ahead.

PERSPECTIVES

Plasma SM and ceramides are synthesized mainly in hepatocytes, where they are packaged into VLDL and other lipoproteins. The distinct changes in plasma ceramide composition in CVD patients may be a result of SMase activity on LDL, with the resulting ceramide playing a critical role in the formation and stability of atherosclerotic plaques. LDL SM and ceramide levels are both elevated in atherosclerotic patients, although the exact mechanism responsible for these changes, as well as their precise effects on atheromatous plaques, is unclear. Since most dietary SLs are excreted in the feces or metabolized to other lipids, it is unlikely that high dietary SL consumption contributes to atherosclerosis and CVD, although further studies are needed to fully understand the contribution of dietary SLs to cardiac and arterial health.

The reason why some, but not all, ceramides predict CVD is unclear. d18:1/C16:0-, d18:1/C18:0- and d18:1/C24:1-ceramides may be less hydrophobic than d18:1/C24:0-ceramide. Upregulation of these ceramides could result in structural changes (i.e., changes in membrane curvature) as well as changes in signaling pathways. Much more work is required to determine how the ceramide acyl chain composition has such disparate prognostic implications for CVD. Of greatest interest is the comparison between ceramides containing C24:0 acyl chains compared to those containing C24:1 chains, and how these relatively similar acyl chains have a different prognostic ability for the development of CVD.

Plasma ceramides appear to be better predictors of CVD than the LDL/HDL ratio. The use of ceramide levels as a biomarker is not yet standard practice and can currently only be performed in a limited number of laboratories worldwide due to the expenses of high-fidelity mass spectrometry and the expertise needed to run such machines. With this in mind, it appears unlikely that the ceramide score will become the standard method of predicting CVD in the near future. However, should more practical methods become available to measure the ceramide score, then it could conceivably become established as the standard for CVD prediction due to its higher prognostic ability.

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